

Response to Arguments

Applicant's arguments filed 12/18/08 have been fully considered but they are not persuasive.

Applicant argues that although Liversidge teaches adjuvants, such as preserving, wetting, emulsifying and dispersing agents, may be added to Liversidge's nanoparticulate active agent composition, Liversidge cautions that the addition of other substances may affect crystal growth. See column 10, lines 23-26, and column 3, lines 6-16. Liversidge distinguishes his invention from the prior art that requires the additional substances to prevent crystal growth. See column 3, lines 10-16. Moreover, nothing in Liversidge suggests that his method of reducing crystal growth with small particle size is in anyway insufficient, non-functional, or requires further improvement: "nanoparticulate [active agent] compositions having an optimal effective average particle size exhibit minimal particle aggregation and crystal growth, even following prolonged storage periods or exposure to elevated temperatures" (Liversidge, column 3, lines 36-40).

However, in response to applicant's arguments, it is noted that although Liversidge cautions that the addition of other substances may affect crystal growth, Liversidge teaches the addition of pharmaceutically acceptable adjuvants such as wetting agent, and dispersing agent. Nothing in Liversidge preclude the addition of mannitol as a wetting agent or dispersing agent. It is well-known in the art that mannitol can be used as a dispersing agent and/or wetting agent. Accordingly, it would have been obvious to one of ordinary skill in the art to, by routine experimentation adding a

wetting or dispersing agent such as mannitol to the composition of Liversidge with the expectation of at least similar result to the claimed invention.

Applicant argues that the Examiner's suggestion to add the crystal growth inhibitor sugars of Straub's to the composition of Liversidge's is without reason and contravenes the teachings of Liversidge. That is, one of ordinary skill in the art would not have any reason to add a crystal growth inhibitor (Straub's sugars) to Liversidge's composition because 1) Liversidge has already solved the problem of crystal growth and Liversidge recommends against adding other substances to the composition for the concerns of side effects and increased cost. The Examiner's reasons to add the sugars in Straub to the composition of Liversidge were that such an addition would result in an "additive effect" and/or "prolonged" stability. The Examiner asserted that "one of ordinary skill in the art would have been motivated to combine surface modifiers, mannitol as an anti-crystallization [agent], and nanoparticle drug with the expectation of [obtaining an] *additive affect [sic, effect]* in preventing crystal growth in nanoparticulate composition [and] to obtain a nanoparticulate composition that exhibit[s] *prolonged* particle size stability even following exposure to elevated temperatures" (final Office Action, page 3, lines 11-15; emphasis added) lacks any factual basis. There is nothing on record, in the prior art, or asserted to be within the knowledge of one of ordinary skill in the art of to support the Examiner's assertion, that combining the teachings of Liversidge and Straub will result in an "additive effect" or "prolonged" stability.

In response to applicant's arguments, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). As discussed above, nothing from Liversidge would prevent the skilled artisan to, by routine experimentation adding a wetting and/or a dispersing agent to the composition of Liversidge. Mannitol is known in the art as a wetting and/or dispersing agent. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Straub is cited for the teaching of mannitol having an additional property such as a crystal growth inhibitor.

Applicant argues that one skilled in the art would not have had any reason to substitute Bagchi's crystal growth modifier, which must possess at least 75% identity in chemical structure to the active agent, for either glycerol as taught by De Gravilla or mannitol as taught by Straub. More specifically, Bagchi describes a laundry list of active agents at column 5, lines 27-55. The Examiner has failed to establish that glycerol or mannitol shares at least 75% identity with any of the listed active agents of Bagchi. Moreover, one skilled in the art would not have immediately envisaged that

glycerol or mannitol shares the required structural similarities with the active agents of Bagchi. Therefore, a reason or motivation to combine the cited references is lacking.

However, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). It is noted that Bagchi teaches surface modifiers is used interchangeably with surfactants, which include a wide range of surfactants such as any known organic and inorganic pharmaceutical excipients. De Gravilla is cited solely for the teaching that glycerol is well known in the art as a surface modifier. With respect to the incorporation of Straub for the teaching of mannitol, it is noted that mannitol besides being a useful excipient, mannitol is also known to be used in medicine industry. See for example, Saha at paragraph 0005 for the teaching that mannitol is used in medicine as a powerful osmotic diuretic or vasodilator. See also Patterson et al. at paragraph 0098. As admitted by applicant, Bagchi teaches a wide variety of active agents which also include diuretics or vasodilators. Accordingly, the burden is shifted to applicant to show that mannitol or CGM taught by Straub does not share at least 75% identity with any of the listed active agents of Bagchi.

/S. Tran/
Primary Examiner, Art Unit 1615

Application/Control Number: 10/619,539
Art Unit: 1615

Page 6